Forming the Hematopoietic Niche from Human Pluripotent Stem Cells

Grant Award Details

Forming the Hematopoietic Niche from Human Pluripotent Stem Cells

Grant Type: Basic Biology III

Grant Number: RB3-05217

Project Objective: Objective of the project is to develop and characterize niche for hematopoietic differentiation. This project is based on PI's earlier work on human mesodermal progenitors (hEMPs)

Investigator:

Name:	Gay Crooks
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Blood Cancer, Cancer

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,252,857

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE (Year 4)

View Report

Grant Application Details

Application Title: Forming the Hematopoietic Niche from Human Pluripotent Stem Cells

Public Abstract:

The clinical potential of pluripotent stem cells for use in regenerative medicine will be realized only when the process by which tissues are generated from these cells is significantly more efficient and controlled than is currently the case. Fundamental questions remain about the mechanisms by which pluripotent stem cells differentiate into mature tissue. The overall goal of this research proposal is to discover if the cell types produced during differentiation of PSC produce the microenvironment needed for specialized tissue stem cells to develop.

To approach this question we will use the hematopoietic ("blood-forming") system as our model, as it is the best characterized tissue in terms of differentiation pathways and offers a range of unique technical tools with which to rigorously study questions of differentiation. Adult hematopoietic stem cells survive and grow in the bone marrow only if they are physically close to specialized cell types, the so-called hematopoietic stem cell "niche". We hypothesize that hematopoietic stem cells are not produced from pluripotent cells because the cells that form the niche and provide the necessary signals are not present during this early stage of differentiation.

Our research proposal has three specific aims. The first aim is to determine if a single cell type derived from pluripotent cells can generate both blood cells and the cells of the hematopoietic niche. The second aim is to identify the types of niche cells produced from pluripotent cells and define how each of them affect the growth of adult stem cells. In the third aim, the cell types that are found in aim 2 to best support adult hematopoiesis, will then be tested for their ability to promote the production of hematopoietic stem cells from pluripotent stem cells.

The findings from these studies will have broad applicability to the production of other types of tissues from pluripotent stem cells, all of which have stem cells that require interaction with a specialized niche. In addition to the biological questions explored in this proposal, our focus on the blood system has direct clinical relevance to the field of bone marrow and cord blood transplantation. The development of a human hematopoietic niche from pluripotent stem cells could potentially be used to expand hematopoietic stem cells from adult tissues like cord blood. Most importantly, the ability to control differentiation from pluripotent stem cells into the blood lineage could provide an unlimited source of matched cells for transplantation for patients with leukemia and other diseases of the bone marrow and the immune system who currently lack suitable donors.

Statement of Benefit to California:

The unique combination of pluripotentiality and unlimited capacity for proliferation has raised the hope that pluripotent stem cells will one day provide an inexhaustible source of tissue for transplantation and regeneration. Diseases that might be treated from such tissues affect millions of Californians and their families. However, much is still to be learned about the mechanisms by which pluripotent stem cells differentiate into mature tissue. The clinical potential of pluripotent stem cells for regenerative medicine will be realized only when the process by which tissues are generated from these cells is significantly more efficient and better controlled than is currently the case.

The research proposed in this application has broad potential benefits for Californians both through the biological questions it will answer and the relevance of these studies for clinical translation. Our goal is to understand the way the microenvironment influences tissue production from pluripotent stem cells, a critical issue for the field of stem cell biology. Specifically we will explore the question- Do the cell types produced during differentiation of pluripotent stem cells produce an adequate microenvironment for the differentiation of tissue or are some cells inhibitory to tissue production? Our approach to these questions will be to use the hematopoietic ("blood-forming") system as our model, as it is the best characterized tissue in terms of differentiation and offers a range of unique technical tools with which to study these questions rigorously. However, the fundamental concepts formed from these studies will have great relevance for the clinical production of other types of tissues from pluripotent stem cells, such as islets, neural cells and cardiac muscle.

In addition to the broad biological questions explored in this proposal, our focus on the blood system has direct clinical relevance to the field of bone marrow and cord blood transplantation. One goal in the proposal is to generate a cellular platform from pluripotent stem cells that will create an environment in which adult blood stem cells can grow and be expanded. Cell numbers collected from cord blood at birth are often insufficient for transplantation in adult patients and older children. The development of a human cell culture system that could expand the number of cord blood stem cells would provide new opportunities for transplantation for patients with leukemia and other diseases of the bone marrow and the immune system who currently lack suitable donors. All scientific findings and technical tools developed in this proposal will be made available to researchers throughout California, under the guidelines from the California Institute of Regenerative Medicine.
